Remarks

Claims 1 and 2 are pending. Claim 1 is amended to recited "differentially removing high molecular weight protein" as supported in the specification at page 5, lines 5-8, page 9, line 19 – page 10, line 26 and page 20, lines 13-15. In light of these amendments applicants respectfully request reconsideration of this application, entry of these amendments and new claims, and allowance of the application to issue. The specification is amended to correct inadvertent typographical errors. It is believed that these amendments add no new matter.

Objections

The Office action states that the Abstract is objected to because of legal language, namely, "comprising." An amended Abstract was included on page 3 of the previous response in response to the same objection. Since this is the currently accepted format for submitting a replacement Abstract, it is not clear what the current objection is based on. In the absence of clarification as to the current basis for objection, applicants are unable to fully address this objection. However, for the examiner's convenience the abstract amendment has been repeated above and a clean copy of the Abstract is attached as Exhibit A

The Office Action states that the specification has not been checked for errors, and notes that applicants filed an amendment in the parent case correcting grammatical and typographical errors. The specification is amended to correct inadvertent typographical errors.

Rejection Under 35 U.S.C § 103

Claim 1 is rejected as allegedly obvious over Georgadze et al.

With respect to the Georgadze et al. the examiner points out that this document describes plasmapheresis treatment which may be used for the treatment of ischemia in the lower extremities of diabetics. In the view of the examiner the reference discloses that the plasmapheresis corrects the biochemical and coagulation parameters of the blood and thereby preserves the extremity from amputation in most patients.

The examiner concludes that with respect to the treatment of the foot it would have been obvious for persons skilled in the art based on the teaching of Georgadze et al. to use plasmapheresis as treatment for persons diagnosed with diabetic ischemia of the foot since the foot is obviously a lower extremity. According to the Examiner, such treatment would be beneficial to preserve the foot from amputation. Regarding the specific removal of high molecular weight protein, the examiner asserts it would have been within ordinary skill to choose a method to remove proteins of any desired size, such as high molecular weight proteins, using the method of Georgadze et al.

Claim 1 recites that the claimed method of treatment differentially removes high molecular weight proteins from the blood. The recitation of this feature illustrates a non-obvious distinction over the cited Georgazde et al. reference.

Georgadze et al. does not suggest the selective removal of large molecular weight proteins in that it fails to mention this approach and it fails to provide any motivation for

selective removal. Furthermore, it can be concluded from the first page 2nd paragraph that the centrifugation plasmapheresis technique described in the Georgadze et al. document leads to the non-selective elimination of numerous types of blood components that can contribute to diabetic ischemia. This procedure is, by its very nature, non-selective. Thus, not only is there no explicit suggestion, there is no implicit suggestion in Georgadze et al. to selectively remove large molecular weight proteins. In contrast, the treatment according to the invention selectively removes high molecular weight proteins and preferably low density lipoprotein, cholesterol, alpha-2-macroglobulin and similar high molecular weight proteins.

Furthermore the reference teaches that a medicament Rheopolyglukin was used as an infusion substance (see page 2, 2nd paragraph of English translation). Such a medicament is not used in the treatment according to the present invention. While this component of the Georgadze et al. method is not stated in the reference to be required for success, it is unpredictable that the method would work without this component. Thus, because the reference used Rheopolyglukin, and suggests its future use (see page 5, item 2 of the Conclusions), the reference does not suggest a method in which it is not used. Since the method of the invention does not use this component, the invention is not suggested by the reference. The current Office Action does not explicitly address this argument previously made by applicants. Since it is relevant to the issue of obvoiusness, the Examiner should address it explicitly.

The present invention uses method steps that differ from and are not suggested by Georgazde et al., namely, that specific high molecular weight proteins are removed from the

blood of the patient. After that, the blood is reinfused into the patient and thereby the diabetic ischemia of the foot is treated. Georgadze et al. has the disadvantage of being less selective than the present invention. As explained above the treatment according to the invention is very selective compared to the gravitational plasmapheresis treatment according to the Georgazde et al. reference.

The conclusion of the in the office action that it was obvious for persons skilled in the art based on the teaching of Georgadze et al. to use plasmapheresis as treatment for persons diagnosed with diabetic ischemia of the foot is wrong for the present claim because Georgadze et al. discloses a totally different plasmapheresis procedure compared to the claimed invention. This procedure discloses a technique in which toxic substances are removed from the blood, but not by the selective removal of large molecular weight protein components of the blood. Since there is no suggestion in Georgadze et al. of any advantage to the selective removal of high molecular weight protein, there is no motivation in this reference to do so. In the absence of such motivation, the art cannot render obvious claim 1.

Claims 1 and 3 are rejected as allegedly obvious over Georgadze et al. in view of Malchesky et al.

There is no motivation in Malchesky et al. to apply its teaching to the method of Georgadze et al. or in the context of diabetic ischemia of a foot. There is also no motivation in Georgadze et al. to apply the teaching of Malchesky et al. to its method or in its context of use. Neither reference is directed to the science or practice of hemorheology. Georgadze et al. is

focused on purification of the blood, not on the improvement of the general state of blood fluidity (hemorheology), which is what the present invention is concerned with. Likewise, Malchesky et al. is directed to the treatment of diseases associated with specific blood solutes, not the general state of blood fluidity. In fact, Malchesky specifically mentions diabetic hypertriglyceridemia, because it is associated with elevated triglycerides (a specific blood solute), but does not mention diabetic ischemia because it would not have been apparent that the methods disclosed would treat diabetic ischemia. Thus, there is no suggestion in Malchesky et al. that the method taught therein would have any relevance to diabetic ischemia. Since there is no suggestion in Georgadze et al. of the relevance of hemorheology in the treatment of diabetic ischemia, and since there is no suggestion in Malchesky of either 1) any value to changing blood fluidity or 2) applicability to diabetic ischemia of a foot, there is no motivation to use the technique of Malchesky et al. to modify the method of Geoargadze et al. to treat diabetic ischemia.

Furthemore, please see the attached letter of Dr. Schmid-Schönbein (attached as Exhibit B). Dr. Schmid-Schönbein is the former Director of the Department of Physiology, University of Aachen, and an internationally recognized expert in rheology. Attached is CV for Dr. Schmid-Schönbein and a list of 198 publications identified on PubMed of which Dr. Schmid-Schönbein is an author (Exhibit C). The attached letter explains the concept of hemorheology and notes the failure of the prior art to suggest its application for the treatment of diseases such as diabetic ischemia of a foot. The letter of Dr. Schmid-Schönbein also acknowledges the

significant contribution of the present invention to the art of treating diabetes.

Furthermore, the fact that others have adopted the method of the claims, means that the present invention satisfies a previously unsatisfied need. See Exhibit D: Richter et al., Extracorporeal fibrinogen adsorption--efficacy, selectivity and safety in healthy subjects and patients with foot ulcers, Transfus Apher Sd. 2002 Feb;26(1): 15-27; and Exhibit E: Klingel et al., Rheopheresis in patients with ischemic diabetic foot syndrome: results of an open label prospective pilot trial, Ther Apher Dial. 2003 Aug; 7(4):444-55.

Since neither reference discloses or suggests any value for changing blood fluidity (hemorheology), neither suggests the aspect of the claimed invention that is missing from the other reference. Because the references taken alone or together do not suggest the application of size-based selective removal of high molecular weight proteins from the bloodto treat diabetic ischemia of a foot, the invention of claims 1 and 2 is not obvious over the art.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $60.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(1)is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Gwendolyn D. Spratt — 12-12-05

Gwendolyn D. Spratt — Date